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A new synthetic route to chiral 3-aryl-5-ethyl-1,4,2-oxazaphosphorines

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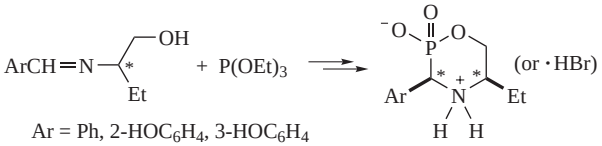
Diastereoselective synthesis of racemic and enantiopure 3-aryl-5-ethyl-1,4,2-oxazaphosphorines, including those bearing phenolic hydroxyl groups in the exocyclic aromatic fragment, was implemented by the reaction of imines derived from (±)- and (*R*)-(–)-2-aminobutan-1-ol and (hydroxy)benzaldehydes with triethyl phosphite and trifluoroacetic acid, followed by the one-pot dealkylation of the intermediate esters.

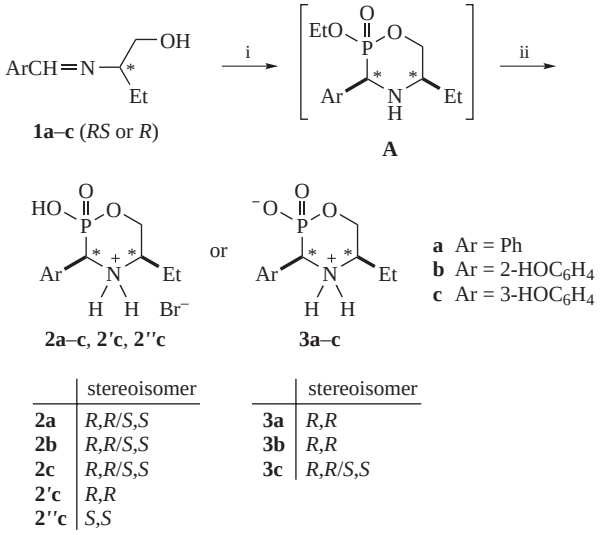


1,4,2-Oxazaphosphorines are interesting phosphorus-containing heterocycles with the O–P–C–N endocyclic fragment, which can be considered as cyclic six-membered α-amino phosphonic acid derivatives. The insertion of the stereogenic carbon and phosphorus atoms into the cycle creates prerequisits for their stereo- and enantioselective synthesis with the formation of various stereoisomers. Since α-amino phosphonic acids are widely used as building blocks for the design of new bioactive molecules,[1] search for the methods of synthesis of 1,4,2-oxazaphosphorines in racemic and enantiomerically pure form, and the study of their structural features is of special interest. Moreover, their structure implies their potential use as organocatalysts as well as ligands for chiral metal complex catalysts.

Previously, 1,4,2-oxazaphosphorines were obtained by the interaction of 1,3,2-oxazaphospholanes with aromatic[2] and aliphatic[3] aldehydes. Their structure was proved by NMR spectroscopy.[4] Later, enantiopure oxazolidines were used in reaction with trimethyl phosphite in the presence of tin tetrachloride to isolate 1,4,2-oxazaphosphorines both in diastereomerically and, for the first time, in an enantiomerically pure form.[5] The reaction of enantiopure amino diols with triethyl phosphite was also used for the synthesis of such heterocycles.[6] Our studies showed[7] that the interaction of imino alcohols with chlorophosphites afforded 1,4,2-oxazaphosphorines, including enantiopure samples. Later, the synthesis of 1,4,2-oxazaphosphorines was carried out by cyclization of both amino phosphonates[8] and amino phosphinates,[9] bearing a hydroxyl group. Note that compounds exhibiting antidepressant activity were found among such amino phosphinates.[10] In view of the aforesaid, a rather limited set of methods for the synthesis of 1,4,2-oxazaphosphorines has been described so far. Most of them involve either hard-to-obtain initial compounds or reagents incompatible with some functional groups.

We have previously reported that the reactions between imines of Betti base [1-(α-aminobenzyl)-2-naphthol] and P^{III} derivatives in the presence of co-electrophiles allowed one to obtain the corresponding α-amino phosphonates under mild conditions with good diastereomeric excess.[11] Assuming that the usage of the imine derivatives of chiral β-amino alcohols in the reaction with trialkyl phosphites and trifluoroacetic acid leads to simultaneous or sequential addition of the corresponding phosphite at the imino alcohol and cyclization, the formation of 1,4,2-oxazaphosphorines can be expected.

To verify this assumption, we first studied the three-component reaction of imine (±)-**1a** derived from benzaldehyde and racemic 2-aminobutan-1-ol with triethyl phosphite and trifluoroacetic acid in the 1 : 1.2 : 2.2 ratio (Scheme 1). To obtain final cyclic amino phosphonic acid, the intermediate esters **A** were treated with the excess of bromotrimethylsilane and further on with methanol. As a result cyclic amino phosphonic acid as hydrobromide salt was isolated, which crystallized from methanol as a single diastereomer (*R*,*R*/*S*,*S*)-**2a** in good yield. The relative configuration of the chiral centers of the product was the same as in 1,4,2-oxazaphosphorine synthesized by us earlier by the reaction of 2-aminobutanol imine derivative with diethyl chlorophosphite.[7(e)] Similarly, enantiomerically pure (*R*,*R*)-**3a** was obtained in a good yield from imine (*R*)-**1a** (see Scheme 1).



	stereoisomer
2a	*R*,*R*/*S*,*S*
2b	*R*,*R*/*S*,*S*
2c	*R*,*R*/*S*,*S*
2′c	*R*,*R*
2′′c	*S*,*S*

	stereoisomer
3a	*R*,*R*
3b	*R*,*R*
3c	*R*,*R*/*S*,*S*

Scheme 1 *Reagents and conditions*: i, $P(OEt)_3$, CF_3CO_2H, CH_2Cl_2, 5→20 °C; ii, Me_3SiBr, 5→20 °C, then MeOH, EtOH or Pr^iOH. Monocrystal of **2′′c** as solvate with Pr^iOH was picked up from conglomerate after crystallization of racemate **2c** from Pr^iOH. Crystals of **3c** were obtained by recrystallization of **2c** from aqueous Pr^iOH causing loss of HBr.

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